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(54) Title: LONG CHAIN ANTIVIRAL COMPOUNDS

(57) Abstract

A long chain compound of formula Z-(A)_n-Y, wherein each of Z and Y is a polyheteroalkyl chain of 9 to 32 members or is a polyheterocyclic moiety having from 9 to 32 ring members, providing that one of Z and Y is a chain, and A is a linking atom or group and n is 0 or an integer from 1 to 6, is indicated as an antiviral compound and has shown activity against HIV in standard tests.

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LONG CHAIN ANTIVIRAL COMPOUNDS

This invention concerns improvements in chemical compounds.
more especially it concerns compounds and pharmaceutical compositions. In
particular it concerns compositions and compounds having activity in in vitro
tests on Human Immunodeficiency Virus-infected cells.

The disease known as Acquired Immune Deficiency Syndrome (AIDS) caused by infection by HIV has attracted immense research effort because of the effects of the disease on infected individuals and the dangers of the disease spreading to a wider section of the population. In general, although various chemo-therapeutic treatments have been advocated, and some compounds have emerged as a potential basis for treatment, there is still a need for alternatives. In particular, most treatments such as the compound

known as AZT have a high toxicity to cells, and it would be desirable to find compounds which are less toxic. In man, the development of resistance to AZT has been identified as an additional clinical problem.

5 We have found a group of compounds which show protective properties in in vitro screens of cells challenged with HIV-1 and/or HIV-2, and are therefore indicated as having potential for the treatment of AIDS and AIDS Related Complex and other viral and especially retroviral infections. Accordingly, the present invention provides the use of compounds defined
10 below, in pharmaceutical compositions for treating HIV-infected patients. The invention further provides pharmaceutical compositions comprising a said compound in combination or association with a pharmaceutically acceptable diluent or carrier, for the treatment of HIV-infected patients. The invention may also be defined as the use of a said compound for the manufacture of
15 a medicament for the treatment of HIV-infected patients. The invention further provides a process for the production of a pharmaceutical composition for the treatment of a HIV-infected patient, comprising the combination of a compound as defined below with a pharmaceutically acceptable diluent or carrier, and formulating said composition into a form suitable for administration to said patient. The invention also provides a method of
20 treatment of an HIV-infected patient, comprising administering to said patient an effective dose of a said compound. It is to be understood that treatment includes prophylactic treatment of patients at risk, in view of the protective properties observed. Whilst this description is especially directed to
25 combating HIV, this invention includes other aspects in which other diseases may be treated, including for example microbial infections.

A 2,2'-dimer of cyclam has been reported as being isolated as a 2% by-product in the synthesis of cyclam (1,4,8,11-tetraazacyclotetradecane) (Barefield et al, J C S Chem Comm (1981), 302). This compound was stated to be insoluble in water. We believe that the insoluble 2,2'-bicyclam is a mixture of the 2R,2'R and 2S,2'S enantiomers; we have characterised a soluble dimer which we believe to be the meso 2R,2'S isomer. The 6,6'-bicyclam isomer has been reported by Fabbrizi et al, Inorg Chém 25, 2671 (1986). Certain N,N'-linked bicyclic compounds have been reported by Ciampolini et al, Inorg. Chem. 26, 3527 (1987). No biological activity has been suggested for such compounds.

US Patent 4,156,683 discloses monocyclic and bicyclic macrocyclic compounds, which are said to have biological activity in regulating sodium, potassium and calcium levels in mammals. Additionally, a specific group of N-alkylated monocyclic compounds are said to possess activity against A₂ influenza viruses in a modified Hermann test on chick fibroblast tissue. The single example mentioned of such N-alkylates/monocyclic compounds is 4,13-dimethyl-1,7,10,16-tetra-4,13-diazacyclooctadecane. It is also said that the preferred compounds, which form complexes of greater stability, are those having three bridging chains between bridgehead nitrogen atoms, that is fused bicyclic compounds.

It is also reported in Chemical Abstracts 88 1052925 (1978) that certain fused triple ring heterocyclic compounds have activity against A₂ England influenza virus in chick embryos.

Rowett et al have reported in Biochem J 1987, 245(3) 641-7, that some simple cyclic polyamines reduce the infectivity of bacteriophages. Bacteriophages infect bacteria but do not cause any human disease, and this paper does not discuss anti-viral activity in humans.

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Certain tetramines have been synthesised and shown to be active in tests indicating antimalarial activity. (Edwards et al, J Med Chem, 34, No 2, 569[1991]).

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Our US Patent 5,021,409 discloses that linked cyclic polyheterocyclic compounds have activity against HIV.

The present invention provides active compounds of the general formula I,

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in which each Z and Y is independently a polyheteroalkyl chain having a chain length of 9 to 32 members or a polyheterocyclic moiety having from 9 to 32 ring members, and each having from 3 to 8 heteroatoms, wherein the heteroatoms are selected from nitrogen, oxygen and sulphur, provided that at least one of Z and Y is a said chain,

A is a linking atom or group, and

n is 0 or an integer from 1 to 6.

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The invention also encompasses acid addition salts and metal complexes of the compounds of formula I.

In the above formula, A may be alkylene, for example 1,3 propandiyl, unsaturated alkylene or a group selected from aryl, alkylaryl, alkylarylalkyl, fused aryl, polyoxoethylene, carboxylate, esters and amides, or a nitrogen or sulphur atom. In a particularly preferred embodiment of the invention, A is alkylene of 1 to 6 carbon atoms or is alkylphenylalkyl in which each alkyl is of 1 to 6 carbon atoms and the phenyl ring is unsubstituted or substituted by methoxy, fluorine, chlorine, bromine or nitro, and the alkyl groups are in the m- or p- positions relative to one another.

The chains or heterocycles Z and Y may be linked to the remainder of the molecule through carbon or heteroatoms, for example linked through C,C',C,N' or N,N'.

Each of Z and Y may contain nitrogen and/or oxygen and/or sulphur heteroatoms; preferably the moieties contain nitrogen atoms with optional further heteroatoms selected from oxygen and sulphur. A particular embodiment of the invention relates to compounds in which all the chain or nuclear heteroatoms are nitrogen atoms. A more preferred embodiment relates to compounds in which each of Z and Y contain four nitrogen atoms.

The chains or cyclic moieties may be substituted or unsubstituted, and may contain unsaturation. Suitable substituents may be selected from halogens, especially fluorine, chlorine or bromine, -NH₂, -OH, -COOH, ester groups, -CONH₂ and alkyl or aryl groups, eg of up to 10 carbon atoms, which themselves may be substituted by the aforementioned substituents. Preferred chains are of 8 to 18 atoms, especially 8 to 16 atoms, preferably with 4 to 8 nitrogen heteroatoms; preferred cyclic moieties

are those of 10 to 24 ring members, especially 12 to 18 ring members, and preferred numbers of nuclear nitrogen atoms are 4 to 6. It is convenient that if two chains are linked, they are identical.

5 The invention also includes what may be termed "pro-drugs".
that is protected forms of the linked compounds, which release the compound
after administration to a patient. For example, the compound may carry a
protective group which is split off by hydrolysis in body fluids, e.g. in the
bloodstream, thus releasing active compound. A discussion of pro-drugs may
10 be found in "Smith and Williams' Introduction to the Principles of Drug
Design", H J Smith, Wright, 2nd Edition, London 1988.

15 The compounds of general formula I are believed to be novel.
They may be prepared by the man skilled in organic syntheses, using a
variety of methods analogous to those already known in the literature. Thus,
Ciampolini et al (Inorg Chem 26, 3527[1987]) have demonstrated the
syntheses of alkyl-linked bicyclams by condensation of N,N',N"-tritosylcyclam
with bis (tosyloxy)alkanes or with bis(acyl chlorides). The syntheses of C,N'-
and N,N'-linked compounds of formula I may be performed in a similar
20 manner by reacting activated precursors (eg compounds substituted with alkyl
chains terminated with halides or activated carboxylates) with (N-1)-substituted
heterocycles (eg N,N',N"-tritosylcyclam) or (N-1)-substituted polyazaalkanes
followed by deprotection.

25 Thus, the invention further provides a process for the production
of compounds of formula I, comprising reacting a compound of formula II
or III,

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in which Z, A and n are as defined above, and

X^1 is a reactive atom or group

5 with a compound of formula IV or V, respectively,



in which Y, A and n are as defined above, and

X^2 is a reactive atom or group.

10 under conditions such that a compound of formula I is formed and the reactive atoms or groups X^1 and X^2 are split off. It will be realised that it may be desirable to protect other reactive sites on the moieties Z and Y, for example amino nitrogen atoms, from participation in unwanted reactions, and this may be done by methods well known to the skilled synthetic chemist, followed by deprotection. Such process variants are to be
15 understood as being within the scope of the invention.

The compounds are indicated for the treatment of viral infections, especially retrovirus infections and particularly HIV infections, and the compounds of formula I, are to be considered as active compounds for the pharmaceutical compositions, processes for making the same and methods of treatment mentioned above. In these aspects of the invention, it is to be understood that meso forms, enantiomers and resolved optically active forms of the compounds of formula I, are included. Also, it is to be considered within the invention, compounds of formula I diluted with non-toxic or with other active substances. Acid addition salts, for example hydrochlorides, and non-toxic labile metal complexes of the compounds of

formula I are also active compounds according to the present invention. Non-toxic in the present context has to be considered with reference to the prognosis for the infected patient without treatment. Zinc and nickel complexes are especially indicated, whereas less labile metal atoms such as cobalt and rhodium are less preferred because of likely lower selectivity.

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The invention will now be described by way of example only.

EXAMPLE 1

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a) N-Tosyl-3-aminopropanoic acid

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To a mixture of 3-aminopropanoic acid (1 equivalent) in water/dioxane (1/1) was added a solution of NaOH (3 equivalents) in water (50% solution). To the vigorously stirred reaction mixture tosyl chloride (1.1 equivalents) was added portion-wise over 3 hours. The reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was washed with ether and the aqueous phase was acidified to pH 2.0 with concentrated HCl. The acidified solution was extracted with ethyl acetate three times. The combined organic extracts were washed with brine, dried over magnesium sulphate, filtered and concentrated to give the desired product as a white solid; m p 118.5-120°C; yield 85%.

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b) Succinimidyl N-tosyl-3-aminopropanoate

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To a solution of N-tosyl-3-aminopropanoic acid (1 equivalent) and N-hydroxysuccinimide (1 equivalent) in ethyl acetate was added dropwise a solution of dicyclohexylcarbodiimide (1 equivalent) in ethyl acetate. The reaction mixture was stirred at room temperature for 4 hours during which time copious amounts of a white precipitate formed. The solids

(dicyclohexylurea by-product) were removed by filtration and the filtrate was concentrated to dryness to give a thick colourless viscous oil. The oil was treated with ether/ethyl acetate (2/1) to cause precipitation of a white solid: yield 72%; m.p. 126-129°C.

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c) meso-1,2,3,4-tetraaminobutane

The tetraamine was synthesised from meso-erythritol according to the method of R.L. Weller, J. Org. Chem. 49, 5150 (1984).

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d) meso-1,2,3,4-tetrakis(N-(N-(3-tosylamido)propanamido)-butane

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To a solution of 1,2,3,4-meso-tetraaminobutane (1 equivalent) in dimethylformamide was added dropwise a solution of succinimidyl N-tosyl-3-aminopropanoate (8 equivalents) in dimethylformamide. The reaction mixture was heated at 50°C for 5 days. The DMF was removed under reduced pressure and dissolved in THF/1N NaOH and stirred overnight during which time a white/yellow solid precipitated which was removed by filtration. The filtrate was washed with water and dried over magnesium sulphate to give 12.0g of a light yellow solid; m.p. 195-197°C; yield 70%; mass spec.

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e) meso-1,2,3,4-tetrakis(N-mesyl-N'-tosyl-1,3-diamino-propyl)butane)

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To a solution of tetraamide-tetratosylate (1 equivalent) as synthesised above in tetrahydrofuran was added borane-tetrahydrofuran complex (1 M; 10 equivalents). The reaction mixture was heated at reflux for 16 hours. The reaction mixture was cooled to room temperature and excess borane was quenched by the addition of methanol. The solution was

concentrated to dryness and more methanol was added and the solution was re-concentrated. The residue was treated with 10% HCl and then basified to pH 12 with 10 N NaOH. The cloudy solution was extracted with ethyl acetate. The combined organic extracts were dried over magnesium sulphate. 5 filtered and concentrated to give an off-white solid. This product is approximately 50% desired tetraamine and was used directly.

The solid was dissolved in dichloromethane and triethylamine (6 equivalents) was added. To the homogenous solution a solution of mesyl chloride (4.5 equivalent) in dichloromethane was added dropwise and the reaction mixture was stirred overnight at room temperature. Dichloromethane 10 and water were added and the phases were separated. The organic phase was washed with 10% HCl and brine, dried over magnesium sulphate and concentrated to give a white amorphous solid. The solid was dissolved in 15 ethyl acetate and passed through a column of silica gel using ethyl acetate as eluant. The eluate was concentrated to dryness to give the desired product as an amorphous solid; overall yield 30%; mass spectrum 1275 (14%), 1197 (100%), 559 (13%).

20 f) meso-1,2,3,4-tetrakis(N-1,3-diaminopropyl)butane

The tetramesyltetratosylate was dissolved in 48% HBr/HOAc and heated at 100°C for 48 hours. The solvents were removed under reduced pressure to give a brown oil. The oil was dissolved in a minimum amount of concentrated HCl and concentrated to give a brown amorphous oil. The 25 product was characterised by its mass spectrum, and designated compound A.

Other compounds considered to be significant in the present invention are:

4.4-(1.3-propanediyl)-bis-1.4.8.11-tetraazadodecane

2.4'-(1.3-propanediyl)-2-rac-tetraazacyclotetradecyl-4'-(1.4.8.11)-tetraazadodecane

5 1.4'-(1.3-propanediyl)-1-tetraazacyclotetradecyl-4'-(1.4.8.11)-tetraazaundecane

2.4'-(1.3-propanediyl)-rac-2-tetraazacyclotetradecyl-4'-(1.4.8.11)-tetraazaundecane

1.4'-(1.3-propanediyl)-1-tetraazacyclotetradecyl-4'-(1.4.8.11)-tetraazadodecane

10 Additionally, the following compounds may be synthesised using methods analogous to those illustrated above and those described in the literature, and are indicated for further testing in the biological fields described below.

4.4'-(1.2-ethanediyl)-bis-1.4.8.11-tetraazadodecane

15 4.4'-(1.4-butanediyl)bis-1.4.8.11-tetraazadodecane

4.4'-(1.5-pentanediyl)-bis-1.4.8.11-tetraazadodecane

4.4'-(1.6-hexanediyl)-bis-1.4.8.11-tetraazadodecane

2.4'-(1.2-ethanediyl)-rac-2-tetraazacyclotetradecyl-4'-(1.4.8.11)-tetraazaundecane

20 2.4'-(1.4-butanediyl)-rac-2-tetraazacyclotetradecyl-4'-(1.4.8.11)-tetraazaundecane

2.4'-(1.5-pentanediyl)-rac-2-tetraazacyclotetradecyl-4'-(1.4.8.11)-tetraazaundecane

2.4'-(1.6-hexanediyl)-rac-2-tetraazacyclotetradecyl-4'-(1.4.8.11)-tetraazaundecane

1.4'-(1.2-ethanediyl)-1-tetraazacyclotetradecyl-4'-(1.4.8.11)-tetraazaundecane

25 1.4'-(1.4-butanediyl)-1-tetraazacyclotetradecyl-4'-(1.4.8.11)-tetraazaundecane

1.4'-(1.5-pentanediyl)-1-tetraazacyclotetradecyl-4'-(1.4.8.11)-tetraazaundecane

1.4'-(1.6-hexanediyl)-1-tetraazacyclotetradecyl-4'-(1.4.8.11)-tetraazaundecane

2.4'-(1,2-ethanediyl)-2-rac-tetraazacyclotetradecyl-4'-(1,4,8,11)-tetraazadodecane
2.4'-(1,4-butanediyl)-2-rac-tetraazacyclotetradecyl-4'-(1,4,8,11)-tetraazadodecane
2.4'-(1,5-pantanediyl)-2-rac-tetraazacyclotetradecyl-4'-(1,4,8,11)-tetraazadodecane
2.4'-(1,6-hexanediyl)-2-rac-tetraazacyclotetradecyl-4'-(1,4,8,11)-tetraazadodecane

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1.4'-(1,2-ethanediyl)-1-tetraazacyclotetradecyl-4'-(1,4,8,11)-tetraazadodecane
1.4'-(1,4-butanediyl)-1-tetraazacyclotetradecyl-4'-(1,4,8,11)-tetraazadodecane
1.4'-(1,5-pantanediyl)-1-tetraazacyclotetradecyl-4'-(1,4,8,11)-tetraazadodecane
1.4'-(1,6-hexanediyl)-1-tetraazacyclotetradecyl-4'-(1,4,8,11)-tetraazadodecane

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EXAMPLE 2

a) To a solution of p-dibromoxylene (2.0g, 7.54mmol) and K₂CO₃ (524mg, 3.77mmol) in 20ml dry CH₃CN was added tritosylcyclam (1.0g, 1.506mmol) in 10ml of dry CH₃CN dropwise over 45 minutes at room temperature. After the reaction mixture had been stirred for 2 hours at room temperature, the solution was concentrated, taken up in CH₂Cl₂ (150ml), washed with H₂O (10ml) and dried over MgSO₄. The organic layer was concentrated and purified by chromatography on silica gel (elution with 5% EtOAc/hexane to 60% EtOAc/hexane) to afford 980mg (77%) of 1-bromomethyl-4-(1-(4,8,11-tritosyl-1,4,8,11-tetraazacyclotetradecyl)methyl)-benzene as a white solid.

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b) To a solution of N,N'-Bis(3-aminopropyl)ethylenediamine (771mg, 4.42mmol) K₂CO₃ (176mg, 1.26mmol) in 20ml of CH₃CN was added 950mg, 0.532mmol of the product of step a) in 10ml of dry CH₃CN dropwise over 1 hour at room temperature. After the reaction mixture had been stirred for 3 hours at room temperature, the solution was filtered and

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the filtrate was concentrated. The excess tetraamine was removed by distillation of the concentrated filtrate on a Kugel Rohr apparatus (100°C; 0.1mm Hg) and the residual oil was then taken up in 100ml of chloroform and washed with 10% sat Na_2CO_3 three times. The organic layers were combined, dried over K_2CO_3 , and concentrated to afford a white solid - 950mg (90%), as an approximate 2:1 mixture of 1-(1-(4,8,11-tritosyl-1,4,8,11-tetraazacyclotetradecyl)methyl)-4-(1-(1.5,8,12-tetraazadodecyl)-methyl)benzene and 1-(1-(4,8,11-tritosyl-1,4,8,11-tetraazacyclotetradecyl)-methyl)-4-(5-(1.5,8,12-tetraazadodecyl)methyl)benzene.

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c) The mixture produced in step b) (420mg, 0.448mmol) was added to 12ml of acetic acid and 6ml of 48%aq HBr (Aldrich) and the solution was stirred for 30 hours at 110-120°C. The red solution was cooled to room temperature and concentrated to a paste. Acetic acid (10ml) was added and the resulting solid was collected by filtration through a sintered glass funnel. The tan-white solid was washed with acetic acid (20ml) and ether (20ml) and dried under vacuum overnight (60°C/0.4mm Hg). A tan-white solid was thus obtained (400mg, 80%) as an approximate 2:1 mixture of 1-(1-(1,4,8,11-tetraazacyclotetradecyl)methyl)-4-(1-(1.5,8,12-tetraaza-dodecyl)methyl)benzene octahydrobromide and 1-(1-(1,4,8,11-tetraazacyclotetra-decyl)methyl)-4-(5-(1.5,8,12-tetraazadodecyl)methyl)benzene octahydrobromide. The products were separated by chromatography, and their structures were confirmed.

EXAMPLE 3

a) To a solution of triethylenetetraamine (346mg, 2.37mmol) and K_2CO_3 (83mg, 0.592mmol) in 20ml of dry CH_3CN was added the product of step a) of Example 2 (250mg, 0.296mmol) in 10ml of dry CH_3CN dropwise over 1 hour at room temperature. After the reaction mixture had been stirred for 16 hours at room temperature, the solution was filtered and the filtrate was concentrated. The excess tetraamine was removed by distillation of the concentrated filtrate on a Kugel Rohr apparatus (100°C; 0.1mm Hg) and the residual oil was taken up in 100ml of chloroform and washed with 10% sat Na_2CO_3 three times. The organic layers were combined, dried over K_2CO_3 and concentrated to afford a white solid 220mg (82%), as an approximate 2:1 mixture of 1-(1-(1,4,7,10-tetraazadecyl)methyl)-4-(1-(1-(4,8,11-tritosyl-1,4,8,11-tetraazacyclotetradecyl)methyl)benzene and 1-(1-(4,8,11-tritosyl-1,4,8,11-tetraazacyclotetradecyl)methyl)-4-(4-(1,4,7,10-tetraazadecyl)methyl)benzene.

b) The product from step a) above (220mg, 0.242mmol) was added to 8ml of acetic acid and 6ml of 48% aq HBr (Aldrich) and the solution was stirred for 30 hours at 110-120°C. The red solution was cooled to room temperature and concentrated to a paste. Acetic acid (10ml) was added and the resulting solid was collected by filtration through a sintered glass funnel. The solid was washed with acetic acid (20ml) and ether (30ml) and dried under vacuum overnight (60°C/0.4mm Hg). A tan-white solid was

thus obtained (120mg, 46%) as an approximate 2:1 mixture of 1-(1-(1,4,7,10-tetraazadecyl)methyl)-4-(1-(1,4,8,11-tetraazacyclotetradecyl)methyl)benzene octahydrobromide and 1-(1-(1,4,8,11-tetraazacyclotetradecyl)methyl)-4-(4-(1,4,7,10-tetraazadecyl)methyl)benzene. The products were separated using chromatography, and their structures were confirmed.

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EXAMPLE 4

a) To a solution of N,N'-Bis(3-aminopropyl)ethylenediaminetetratosylate (467mg, 0.592mmol) and K₂CO₃ (33mg, 0.236mmol) in 15ml of dry DMF was added 100mg (0.118mmol) of the product of step a) of Example 2 in 10ml of dry DMF dropwise over 1 hour at 60°C. After the reaction mixture had been stirred for 2 hours at 60°C the solution was cooled to room temperature and concentrated. The residual oil was taken up in CH₂Cl₂ (50ml) and washed with (5ml). The organic layer was dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica gel (elution 2% MeOH; 98% CH₂Cl₂) to afford 110mg (60%) of 1-(1-(1,4,8,11-tetratosyl-1,4,8,11-tetraazacyclotetradecyl)methyl)-4-(1-(1,5,8,12-tetratosyl-1,5,8,12-tetraazadodecyl)methyl)benzene, a white solid.

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b) 80mg (0.051mmol) of the product of step a) above was added to 6ml acetic acid and 4ml of 48% aq HBr (Aldrich) and the solution was stirred for 48 hours at 110-120°C. The brown solution was cooled to room temperature and concentrated to a paste. Acetic acid (8ml) was added and the resulting solid was collected by filtration through a sintered glass funnel. The solid was washed with acetic acid (10ml) and ether (10ml) and dried under vacuum overnight (60°C/0.4mm Hg). A tan-white solid 50mg

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(88%), of 1-(1-(1,4,8,11-tetraazacyclotetradecyl)methyl)-4-(1-(1,5,8,12-tetraazadodecyl)- methyl)benzene octahydrobromide was thus obtained and its structure was confirmed.

5 Characterised samples of compound A were tested in the standard in vitro tests, described below.

The compound of the invention was tested in a screen by the MTT method (J.Virol. Methods 120: 309-321 [1988]). MT-4 cells (2.5×10^4 / well) were challenged with HIV-1 (HTLV-IIIB) or HIV-2 (LAV-2 ROD) at a concentration of 100 CCID₅₀ and incubated in the presence of various concentrations of the test compounds, which were added immediately after challenge with the virus. After 5 days culture at 37°C in a CO₂ incubator, the number of viable cells was assessed by the MTT (tetrazolium) method. Antiviral activity and cytotoxicity of the compounds are expressed in the table below as ED₅₀ (ug/ml) and CD₅₀ (ug/ml), respectively. The potential therapeutic usefulness was assessed by calculating a Selectivity Index (SI) corresponding to the ratio of CD₅₀ to ED₅₀. A control test was performed using the known anti-HIV treatment AZT.

20

In the table below, the compounds screened were compound A and the known compound AZT.

TABLE

Compound	Virus	CD ₅₀	ED ₅₀	SI
A	HIV-1	>500	39	>13
	HIV-2	>500	39	>13
AZT (Comparison)	HIV-1	> 1	<0.008	>125

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In this field of study, it is considered that any compound exhibiting a Selectivity Index of greater than 5 has the potential for further study. HIV is one of the most challenging viruses to combat, and the results given above provide an indication of activity against other retroviruses and against other viruses in general. The compounds of the invention are also to be considered for activity against microorganisms, such as bacteria and especially against the organisms causing malaria.

The active compounds may be administered in the form of pharmaceutical compositions formulated according to well known principles and incorporated the compound, preferably in unit dose form, in combination with a pharmaceutically acceptable diluent or excipient. Such compositions may be in the form of solutions or suspensions for injection, or irrigation or be in capsule, tablet, dragee, or other solid composition or as a solution or suspension for oral administration or formulated into pessaries or suppositories or sustained release forms of any of the above for implantation. Suitable diluents, carriers, excipients and other components are known. It may be desirable also to formulate a composition for topical administration such as an ointment or cream. The compounds of the invention may be used, in the form of a composition or alone, and possibly carried on a finely divided

form of a composition or alone, and possibly carried on a finely divided support, as a coating on devices which in use contact body fluids, to discourage transmission of viral infections. Examples of devices to be considered in this aspect of the invention are surgical devices and gloves and contraceptions such as condoms, and other items, appliances, wound dressings and coverings, implements etc generally to be considered as devices according to this aspect of the invention.

The pharmaceutical compositions according to the invention may contain unit dosages determined in accordance with conventional pharmacological methods, suitably to provide active compounds in the dosage range in humans of from 0.1 to 100 mg/kg body weight per day, in a single dose or in a number of smaller doses. Preferred dosage ranges are 1 to 30 mg/kg body weight per day. Other active compounds may be used in the compositions or such active compounds or supplemental therapy may be included in a course of treatment.

CLAIMS:

1. Compounds of general formula I.



5 in which each Z and Y is independently a polyheteroalkyl chain having a chain length of 9 to 32 members or a polyheterocyclic moiety having from 9 to 32 ring members, and each of Z and Y having from 3 to 8 heteroatoms selected from nitrogen, oxygen and sulphur, provided that at least one of Z and Y is a said chain,

10 A is a linking atom or group, and
n is O or an integer from 1 to 6,

and their acid addition salts and metal complexes.

15 2. A compound according to claim 1, wherein one of Z and Y is a polyheterocyclic moiety as defined therein.

3. A compound according to claim 1 or 2, wherein all the heteroatoms in Z and Y are nitrogen atoms.

20 4. A compound according to claim 1, 2 or 3, wherein A is selected from the group consisting of alkylene, aryl, alkylaryl and alkylarylalkyl.

25 5. A compound according to any one of the preceding claims, wherein when Z and/or Y is a chain, the chain length is of 8 to 16 atoms

and when Z and/or Y is a polyheterocyclic moiety, there are from 12 to 18 ring members.

6. A compound according to any one of the preceding claims.
5 wherein the number of heteroatoms in a chain is from 4 to 8, and the number of heteroatoms in a cyclic moiety is from 4 to 6.

7. A compound according to claim 6, wherein, each of Z and Y has four nitrogen atoms as the heteroatoms.

10

8. A compound according to any one of the preceding claims, wherein A is alkylene of 1 to 6 carbon atoms or is alkylphenylalkyl in which each alkyl is of 1 to 6 carbon atoms and the phenyl ring is unsubstituted or substituted by methoxy, fluorine, chlorine, bromine or nitro, and the alkyl groups are in the m- or p- positions relative to one another.

15

9. The compound of claim 1 which is meso-1,2,3,4-tetrakis(N-1,3-diaminopropyl)butane.

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10. The compound of claim 1 which is 1-(1-(1,4,8,11-tetraazacyclotetradecyl)methyl)-4-(1-(1,5,8,12-tetraazadodecyl)methyl)benzene octahydrobromide.

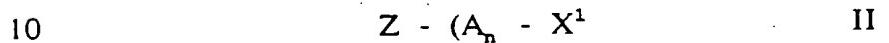
25

11. The compound of claim 1 which is 1-(1-(1,4,8,11-tetraazacyclotetradecyl)methyl)-4-(5-(1,5,8,12-tetraazadodecyl)methyl)benzene octahydrobromide.

12. The compound of claim 1 which is 1-(1-(1,4,8,11-tetraazacyclotetradecyl)methyl)-4-(4-(1,4,7,10-tetraazadecyl)methyl)benzene octahydrobromide.

5 13. A pharmaceutical composition comprising a compound according to any one of the preceding claims, in admixture with or in association with a pharmaceutically acceptable diluent or carrier.

14. A process for the production of a compound according to claim 1, comprising reacting a compound of formula II or III,



in which Z, A and n are as defined above, and

X^1 is a reactive atom or group

with a compound of formula IV or V, respectively,



in which Y, A and n are as defined above, and

X^2 is a reactive atom or group,

under conditions such that a compound of formula I is formed and the reactive atoms or groups X^1 and X^2 are split off.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	JOURNAL OF MEDICINAL CHEMISTRY vol. 34, no. 2, February 1991, U.S.A. pages 569 - 574; M.L. EDWARDS: 'Antimalarial Polyamine Analogues.' cited in the application * the whole article *	1-14
A	CHEMICAL ABSTRACTS, vol. 88, no. 15, 10 April 1978, Columbus, Ohio, US; abstract no. 105292S, ZIMENKOVSKII, B.S.: 'Synthesis and properties of tetraazamacrosanes and their derivatives.' page 570 ; column 1 ; cited in the application see abstract & FARM. ZH. (KIEV) vol. 6, 1977, UKRAIN pages 31 - 37;	1-14
A	US,A,4 156 683 (J.M. LEHN) 29 May 1979 cited in the application see claims	1-14
P,X	US,A,5 021 409 (B.A. MURRER ET AL.) 4 June 1991 cited in the application see claims	1-14
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ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. GB 9200438
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This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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